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ORIGINAL ARTICLE

# A study of redox properties of hydralazine hydrochloride, an antihypertensive drug

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**KEYWORDS**

Hydralazine hydrochloride;
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Spectrophotometric analysis

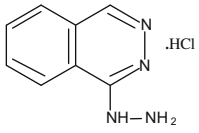
**Abstract** Hydralazine hydrochloride itself is a reducing agent and its redox properties like other reducing agents vary as the oxidizing agent and applied conditions vary. The redox properties of hydralazine were studied by spectrophotometric method. Formal redox potential of hydralazine was calculated and effect of pH was observed on redox properties of hydralazine.



## 1. Introduction

Oxidation reduction is a process which involves exchange of electrons from a reducing agent to an oxidizing agent. The oxidized and reduced species in a half reaction form a redox couple (Housecroft and Constable, 2006).

Hydralazine is an antihypertensive drug with brand names of Apo-Hydral, Apresoline, Novo-Hylazin, Apo-Hydralazine, etc. (Katherine, 2004; Champe and Harvey, 2000). It has antioxidant activity and known for in vitro generation of reactive species of oxygen (ROS), nitrogen (RNS) and prostaglandin (PG) (Daiber et al., 2005; Leiro et al., 2004; Carmody and Anderson, 2007). It is a white to off-white, odorless crystalline powder. It is soluble in water, slightly soluble in alcohol, and very slightly soluble in ether and melts at about 275 °C, with decomposition. It has p$K_a$ value 7.3. Its chemical name is 1-hydrazinophthalazine monohydrochloride and has the following structure (Clark's, 1986; Merck Index, 1997).




There are number of techniques used for the determination of redox potential. Here we used spectrophotometeric technique for redox study.

The redox potential of hydralazine hydrochloride was determined by using potassium ferricyanide complex ($K_3[Fe(CN)_6]$). This complex is colored with ferric and colorless with ferrous. The addition of hydralazine reduced ferric ($Fe^{3+}$) into ferrous ($Fe^{2+}$) and decreased the absorbance of

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the complex. From the change in absorbance the extent of reduction was determined.

The concentration of reduced and oxidized species can be calculated as follows:

$$[\text{Fe(III)complex}]_{\text{eq}} = \frac{\text{Absorbance}}{\varepsilon}$$

$$[\text{Fe(II)complex}]_{\text{eq}} = [\text{Fe(III)complex}]_{\text{total}} - [\text{Fe(III)complex}]_{\text{eq}}$$

$$[\text{Hydralazine}]_{\text{oxidized form}} = [\text{Fe(II)}]_{\text{eq}}$$

$$[\text{Hydralazine}]_{\text{eq}} = [\text{Hydralazine}]_{\text{total}} - [\text{Hydralazine}]_{\text{oxidized}}$$

These values can be used to calculate the equilibrium constant, $K_{\text{eq}}$, where,

$$K_{\text{eq}} = \frac{[\text{Fe(II)}]_{\text{eq}}[\text{Hydralazine}]_{\text{oxidized}}}{[\text{Fe(III)complex}]_{\text{eq}}[\text{Hydralazine}]_{\text{eq}}}$$

The equilibrium constant for oxidation–reduction equilibrium can be calculated from the standard cell potential of the reaction, which in turn may be calculated from the standard electrode potential for the half reactions.

The change in standard Gibbs free energy for the reaction is given by the equation:

$$G^0 = -nFE^0 \quad (1)$$

And $\Delta G^0$ is related to the equilibrium constant by the equation

$$\Delta G^0 = -RT\ln K \quad (2)$$

An expression that relates the equilibrium constant directly to the cell potential is obtained by combining Eqs. (1) and (2) (Christian, 2004; Mortimer, 1991),

$$E^0 = -\frac{RT}{nF}\ln K_{\text{eq}} \quad (3)$$

With the help of this expression formal redox potential or redox equivalent of hydralazine can be calculated by using the formal redox potential of $Fe^{(III)}/Fe^{(II)}$ half cell in the $K_3[Fe(CN)_6]$ complex, by using the following relationship (Robert et al., 2004):

$$E^0_{\text{cell}} = E^0_{\text{oxi}} - E^0_{\text{red}} \quad (4)$$

The reduction of Fe(III)–hydralazine complex was studied by addition of ascorbic acid.

Ascorbic acid is a mild reducing agent and a weak acid, while the radical $HA^-$ is a very strong acid. The binegative ene-diol anion of ascorbic acid, $L^{2-}$, is a bidentate ligand and is capable of reacting with metal ions $M^{n+}$ of coordination number 4 or 6 to form complexes. It is a strong two-electron reducing agent that is readily oxidized in one-electron steps by metal ions and metal complexes in their higher valence states. The first step in the reaction is the formation of monoprotonated Fe(III) complex. This short lived intermediate rapidly undergoes an intermolecular one-electron transfer to give a deprotonated Fe(II) complex of the ascorbate redical anion. The complex dissociates to a free radical anion, which may then combine with a second ferric ion, which in turns undergoes a second intramolecular electron transfer to give the final product dehydroascorbic acid (Martell, 1982).

## 2. Materials and methods

All the chemicals used were of analytical grade, and employed without further purification. All the volumetric glassware used was of standard quality. Special care was taken to wash them thoroughly before use. For this study $CO_2$ free water was used which was prepared by boiling distilled deionized water for 10 min and then cooling it in airtight flask (Cox, 1995).

Shimadzu spectrophotometer, model UV-160A, was used to record spectra and for the measurement of change in absorbance of complex. Three types of spectrophotometric titrations were performed in order to study the redox properties of hydralazine. In first set of experiment titration of potassium ferricyanide was performed with hydralazine. The measurements were taken at the $\lambda_{\max}$ (420 nm) of potassium ferricyanide complex. 0.001 M $K_3[Fe(CN)_6]$ solution and 0.01 M hydralazine hydrochloride solutions were prepared in 0.1 M solution of $KNO_3$. In this titration, twelve volumetric flasks were taken and then numbered. Complex (2.0 mL) was taken in each flask. Different volumes from 0 to 15.0 ml of hydralazine solution were added in respective flasks, and volume was made with 0.1 M $KNO_3$. Temperature was maintained at 25 °C by thermostat. These solutions were then subjected to spectrophotometric analysis and change in absorbance was noted until it became constant.

In second set of experiment reduction of potassium ferricyanide complex was studied by ascorbic acid following the same procedure.

In third set of experiment Fe(III)–hydralazine complex was treated with ascorbic acid. The experiment was repeated at pH 3.0, 5.0, 7.0 and 8.0.

## 3. Results and discussion

In the spectrophotometric titration of potassium ferricyanide with hydralazine, absorbance of the potassium ferricyanide complex decreased gradually with the addition of hydralazine (Fig. 1). The redox equivalent of hydralazine was determined by the data available from spectrophotometric titration. The

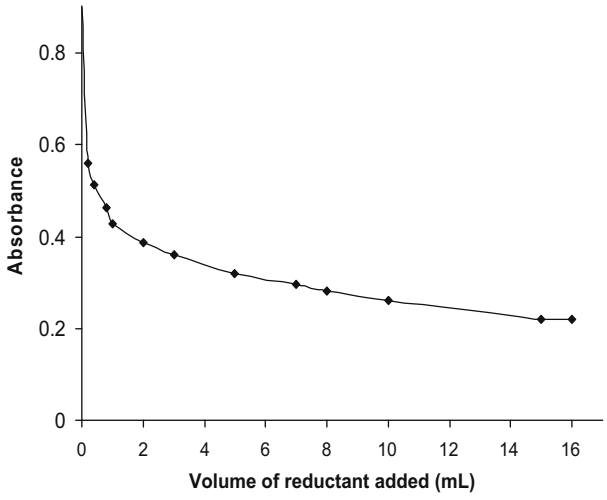


**Figure 1** Spectrophotometric titration of $K_3[(Fe(CN)_6]$ (0.001 M) with hydralazine hydrochloride (0.01 M) at 25 °C.

**Table 1** Redox potential values of hydralazine hydrochloride as determined by spectrophotometric titration.

| Absorbance | $[Fe(III)]_{eq}$ | $[(Fe(II)]_{eq}$ | $[Red]^{-}_{eq}$ | $[Red]^{0}_{eq}$ | $K_{eq}$ | $E^0$ |
|---|---|---|---|---|---|---|
| 0.904 | – | – | – | – | | |
| 0.559 | 1.10E−03 | 9.02E−04 | 1.10E−03 | 9.02E−04 | 0.675 | +0.335 |
| 0.512 | 1.00E−03 | 9.95E−04 | 1.00E−03 | 9.95E−04 | 0.981 | +0.357 |
| 0.462 | 9.06E−04 | 1.09E−03 | 9.06E−04 | 1.09E−03 | 1.46 | +0.380 |
| 0.427 | 8.38E−04 | 1.16E−03 | 8.38E−04 | 1.16E−03 | 1.92 | +0.397 |
| 0.426 | 8.53E−04 | 1.16E−03 | 8.53E−04 | 1.16E−03 | 1.94 | +0.397 |
| 0.408 | 8.00E−04 | 1.00E−03 | 8.00E−04 | 1.00E−03 | 2.25 | +0.406 |
| 0.350 | 6.86E−04 | 1.31E−03 | 6.86E−04 | 1.31E−03 | 3.66 | +0.435 |
| 0.315 | 6.18E−04 | 1.38E−03 | 6.18E−04 | 1.38E−03 | 5.01 | +0.453 |
| 0.305 | 5.98E−04 | 1.40E−03 | 5.98E−04 | 1.40E−03 | 5.49 | +0.459 |
| 0.276 | 2.71E−04 | 1.45E−03 | 2.71E−04 | 1.45E−03 | 29.07 | +0.557 |
| 0.221 | 1.88E−04 | 2.45E−03 | 1.88E−04 | 2.45E−03 | 13.07 | +0.519 |
| | | | | | Average = | +0.469 V |

formal redox potential of potassium ferricyanide is +0.358 V (Dean, 1973).

By means of the data obtained the concentration of complex and other species was deduced and the equilibrium constant ($K_{eq}$) was calculated. $E^0_{cell}$ was calculated using Eq. (3).

$E^0_{red}$ of the complex was calculated using Eq. (4).

The formal redox potential of Hydralazine was found to be +0.469 V (Table 1).

Titration of potassium ferricyanide complex with ascorbic acid was performed in order to compare both hydralazine and ascorbic acid (Fig. 2).

The addition of hydralazine in potassium ferricyanide complex causes a decrease in absorbance. Decrease in the absorbance of the complex is faster in case of ascorbic acid as compared to hydralazine (Figs. 1 and 2). It shows that ascorbic acid is good reducing agent than hydralazine.

Titration of hydralazine with ascorbic acid was performed at pH 3.0, 5.0, 7.0 and 8.0. Before studying the redox properties at different pH Fe(II)–hydralazine and Fe(III)–hydralazine complexes were prepared in solutions of different pH and scanned (Figs. 3 and 4). Spectra of both at pH 3 show that the formation of Fe(II)–hydralazine is very slow at pH 3.0, while it increases at pH 4.0 and above. Formation of Fe(III)–hydralazine is fast at pH 3.0 (Fig. 5).

The data obtained from the addition of ascorbic acid in Fe(III)–hydralazine complex at different pH shows that decrease in the absorbance of Fe(III)–hydralazine complex slows down on increasing pH. As Fe(II)–hydralazine complex for-

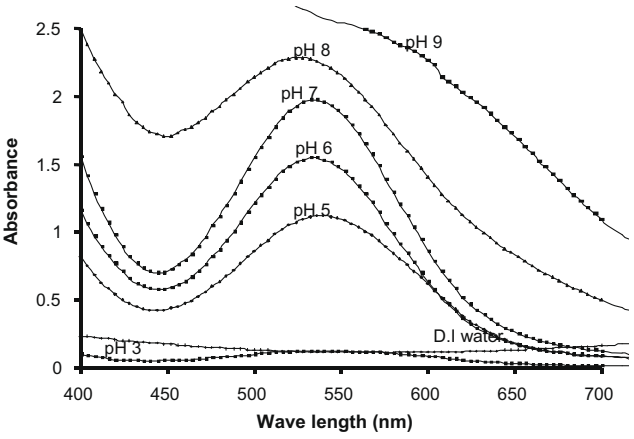


**Figure 3** Effect of pH on Fe(II)–hydralazine complex (1:7 ML ratio).

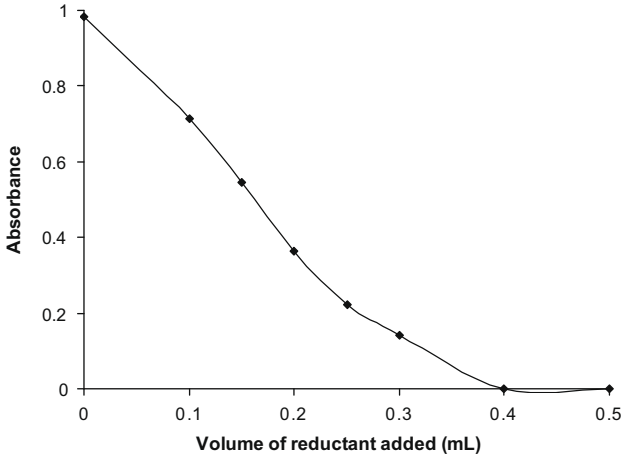


**Figure 2** Spectrophotometric titration of $K_3[(Fe(CN)_6]$ (0.001 M) with ascorbic acid (0.01 M) at 25 °C.

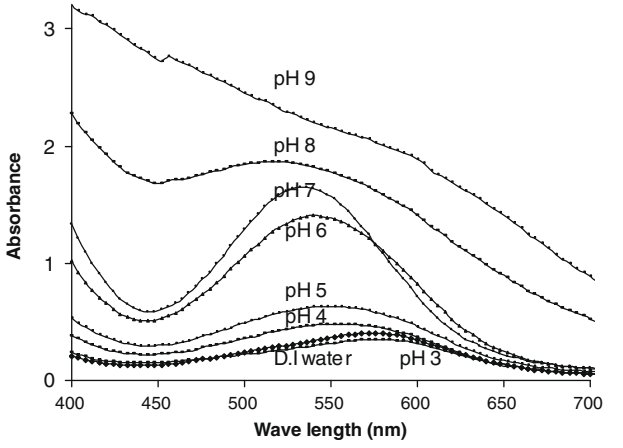


**Figure 4** Effect of pH on Fe(III)–hydralazine complex (1:7 ML ratio).

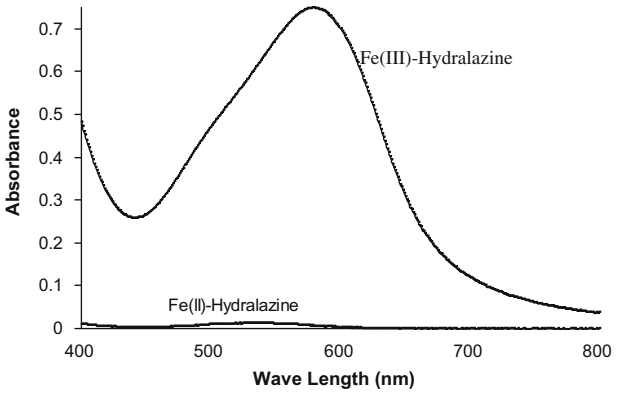


**Figure 5** Spectra of Fe(II)–hydralazine and Fe(III)–hydralazine at pH 3.0 after 30 min.

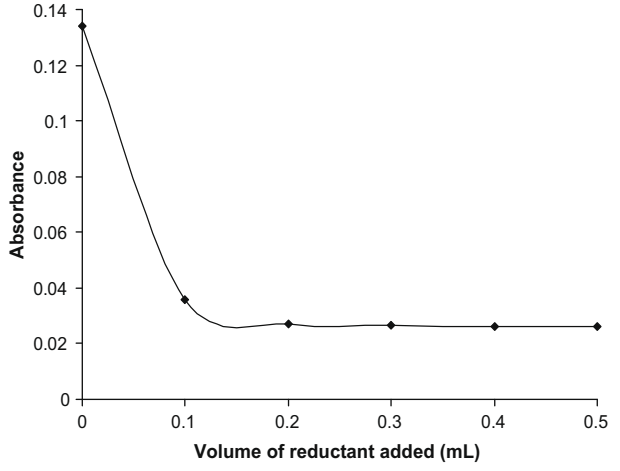


**Figure 6** Spectrophotometric titration of Fe(III)–hydralazine complex by ascorbic acid at pH 3.0.

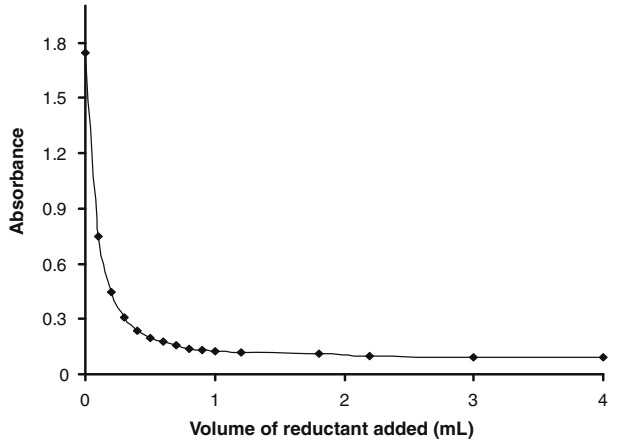


**Figure 7** Spectrophotometric titration of Fe(III)–hydralazine complex by ascorbic acid at pH 5.0.

mation starts near pH 4.0. So at pH 3.0 Fe(III)–hydralazine complex contains most of the oxidized form of Fe(III), which can be easily reduced. So at pH 3.0 ascorbic acid is undergoing

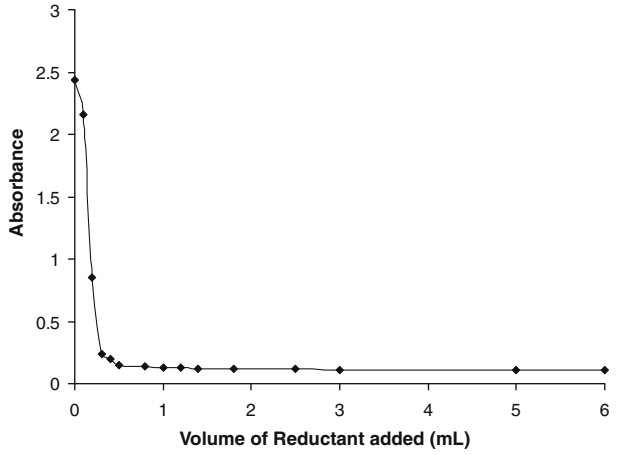


**Figure 8** Spectrophotometric titration of Fe(III)–hydralazine complex by ascorbic acid at pH 7.0.

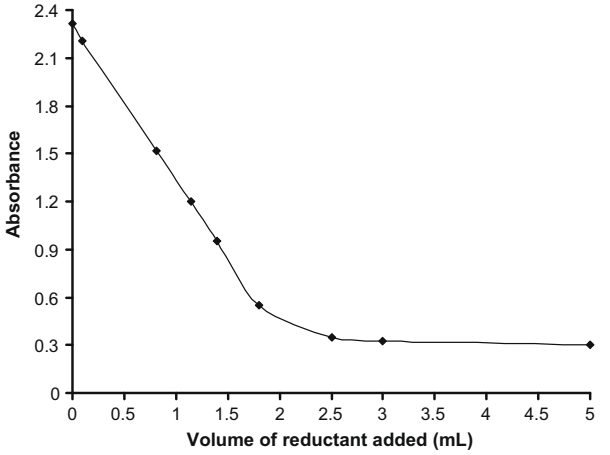


**Figure 9** Spectrophotometric titration of Fe(III)–hydralazine complex by ascorbic acid at pH 8.0.

two types of reactions, i.e., reduction as well as substitution (Fig. 6). At pH 5.0 most of the Fe(III) in the complex is reduced to Fe(II) by hydralazine. As at pH 5.0 the rate of formation of Fe(II)–hydralazine is faster as compared to pH 3.0 (Fig. 3). That is why substitution of hydralazine by ascorbic acid slows down as the pH increases (Fig. 7). The same was observed even at higher pH (Figs. 8 and 9). The reduction study with ascorbic acid shows that at lower pH values Fe(III)–hydralazine complex exists in good amount and ascorbic acid undergoing two reactions, reduction and substitution. While at high pH values ascorbic acid is involved only in substitution reaction.

## References

Carmody, M.S., Anderson, J.R., 2007. Cardiol. Rev. 15 (1), 46–53.
Champe, P.C., Harvey, R.A., 2000. Lippincotts Illustrated Reviews: Pharmacology, second ed. Lippincott Williams and Wilkins, Philadelphia, p. 190.
Christian, G.D., 2004. Analytical Chemistry. John Wiley & Sons, Singapore, pp. 191–193.
Clark's, 1986. Hydralazine, Analytical and Toxicological Data, pp. 662–663.

Cox, P.A., 1995. The Elements on Earth: Inorganic Chemistry in the Environment. Oxford University Press, New York, pp. 166–167.

Daiber, A., Munzel, T., Oelze, M., Coldewey, M., Kaiser, K., Huth, C., Schildknecht, S., Bachschmid, M., Nazirisadeh, Y., Ullrich, V., Mulsch, A., 2005. Biochem. Biophys. Res. Commun. 338 (4), 1865–1874.

Dean, J.A., 1973. Lange's Handbook of Chemistry. McGraw Hill Inc., USA (Sections 6 and 6.5).

Housecroft, C.E., Constable, E.C., 2006. An Introduction to Organic, Inorganic and Physical Chemistry, third ed. Pearson Education Limited, pp. 575–577.

Katherine, M.H., 2004. In: Dart, R.C. (Ed.), Medical Toxicology, third ed. Lippincott Williams and Wilkins, Philadelphia, pp. 714–715.

Leiro, J.M., Alvarez, E., Arranz, J.A., Cano, E., Orallo, F., 2004. Intern. Immunopharmacol. 4 (2), 163–177.

Martell, A.E., 1982. Chelates of ascorbic acid. In: Seib, P.A., Tolbert, B.M. (Eds.), Ascorbic Acid, Chemistry, Metabolism and Uses. American Chemical Society, Washington, DC, USA, pp. 153–158.

Mortimer, R.G., 1991. Physical Chemistry. The Benjamin Cummings Publishing Company Inc., Tokyo, pp. 298–303.

Robert, K., Jean-Michel, M., Matthias, O., Miguel, V., Michael, W.H. (Eds.), 2004. Analytical Chemistry, second ed. Wiley-VCH, Verlag GmbH and Co., Germany, pp. 318–332.

The Index Merck, 1997. 12th ed., Merck Co. Inc., USA, p. 815.